

Supplementary Online Content

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We provide details associated with randomization, treatment of missing data, and selection bias aspects of the trial. Furthermore, we note some observations on subgroups in our data.

eAppendix 1: Randomization

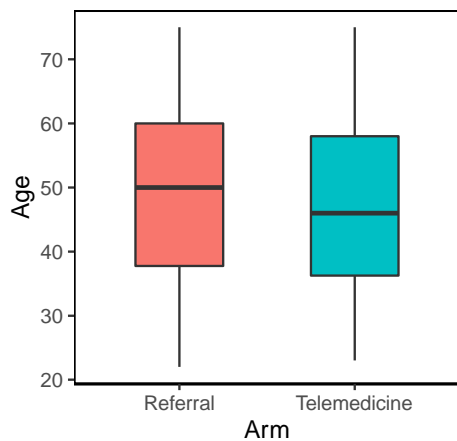
We used covariate-constrained randomization. Details on our randomization scheme are presented in¹ (specifically Sections 3.2 and A.1.2 of Appendix A). Here, we note that the covariates used in the randomization are age, sex, race and ethnicity. All covariates used in the randomization are cluster level covariates. Li et al (2017) have shown that covariate-constrained randomization reduces power loss for redundant analysis-based adjustment for non-prognostic covariates.²

To control for differential recruitment and avoid arm contamination, we implemented a variety of procedures. The randomization schedule was kept confidential. Sites were notified 30 days prior to cross-over to the intervention. All other sites were unaware of the randomization schedule. We minimized bias as neither the sites nor the potential participants were aware when the intervention would occur at their sites. Sites strictly adhered to the randomization schedule. Participants who were motivated to be treated were enrolled first and no warehousing of potential participants occurred. Furthermore, we maintained lists of individuals participating in the usual care and opioid treatment program (OTP)-integrated facilitated telemedicine arms to avoid usual care participants entering into the telemedicine arm.

As an example of the effect of randomization on the characteristics associated with the obtained sample, we present eFigure 1.

eFigure 1 presents boxplots associated with the age distribution in referral (i.e., usual care [UC]) and OTP-integrated facilitated telemedicine arms. Differences in medians (means) between the two arms are not statistically significant (p-value = 0.60). Furthermore, Table 1 of the main document illustrates the balance between the two arms in terms of sex, race, and ethnicity. Notice that the variable referring to residence location (i.e., rural versus urban) is also balanced between the arms.

eFigure 1: Age distributions at baseline (N= 602) between referral (red) and opioid treatment program-integrated facilitated telemedicine (blue) in both study arms.



eAppendix 2: Treatment of Missing Data

We define “dropouts” as participants who terminated HCV treatment (in either the referral or OTP-integrated facilitated telemedicine arms) before obtaining a sustained virological response (SVR) determination. In the referral arm, 186 participants and in OTP-integrated facilitated telemedicine, 22 participants, did not have a treatment start date. Furthermore, 18 participants in usual care and 17 in OTP-integrated facilitated telemedicine initiated treatment but dropped out of the study for various reasons. Therefore, the final rate is 243/602=40.36%. Furthermore, individuals in both arms were provided 5 months to undergo an HCV evaluation to initiate treatment. In chronic HCV infection, spontaneous HCV resolution occurs at 0.36% person years.³

eTable 1 presents the number of individuals who terminated study participation prematurely and the associated reasons for early termination. There were 18 dropouts in usual care and 17 in OTP-integrated facilitated telemedicine. Since the missing mechanism is assumed to be “missing at random” (MAR), we utilized multiple imputation using the R package “MICE (Version 3.15.0)-Multivariate Imputation by Chained Equations” to generate 20 different imputed data sets per arm.⁴

eTable 1: Reasons for early termination of study participants by study arm among participants with a treatment start date.

Discontinuation Reasons	Referral	Telemedicine	Total
Discharge from MMTP	9	8	17
Incarceration	2	2	4
Loss of insurance	1	0	1
Medication side effects	1	0	1
Other	1	5	6
Death	2	1	3
Relocation	2	1	3
Total	18	17	35

Because SVR is a binary outcome, we use logistic regression to obtain the imputed SVR values. The logistic regression model we constructed includes the following variables: an indicator variable, denoted treatment start date (TSD), that specifies whether the participant had a treatment start date (the value is 1) or not (value is 0), age, sex, race, ethnicity, urban/rural residence location, Drug Abuse Screening Test (DAST10), number of months enrolled in the methadone program, comorbid conditions, alanine aminotransferase to platelet ratio index (APRI), prescription drugs used for non-medical reasons, illicit drugs, arm, period, interaction of DAST10 with number of months in the methadone program, and site (as a fixed effect to account for clustering). We follow the principle that the imputation model is neither intended to provide a parsimonious description of the data nor does it represent structural or causal relationships among the variables. It is merely a device to preserve important features of the joint distributions in the imputed variables.⁵ Furthermore, the variables incorporated in the model are thought to influence the rate of missingness.

eAppendix 2.1: Justification of Variables Included in the Model

The justification of incorporating these variables in the imputation model is as follows:

- Arm: Chronic HCV infection has spontaneous occurrence rate at < 0.36% person-years.³
Pooled HCV incidence is 12.1 per 100 person*years.⁶ Younger age, female gender, longer duration of follow-up, longer duration of injection drug use (IDU), and >80% injection in the cohort were associated with increased HCV incidence.
- Age: Most substance users in high income countries are older. Younger people only make up 15% of the injecting population.⁷

Sex: Globally, 2.8 million women and 12.1 million males inject drugs. In North America, 2.3 million men compared to 1 million women.⁷

Race: African-Americans are twice as likely to be infected with HCV compared to other races.⁸
HCV-associated death rates among non-Hispanic Black people are 1.8 times higher than among non-Hispanic white people.⁸

Non-Hispanic Black persons involved more with HCV.⁹

Ethnicity HCV treatment rates are lower in Hispanic individuals compared with non-hispanics.¹⁰

- Compared with Caucasians, Latinx individuals tend to initiate HCV treatment less frequently, discontinue treatment, become infected younger, and have higher reinfection rates.¹¹
- An older study from the interferon era also showed that even though Hispanic individuals were more likely to meet criteria for antiviral therapy, they were less likely to initiate treatment, were more likely to discontinue early, and tended to have lower SVR rates.¹²

DAST10: 66% of acute HCV infections occur in injection drug users.⁸

- Opioids are used by 83% of the world's injection drug users.⁷

Comorbid conditions

People with substance use disorders are more likely to have co-existing mental health issues.⁸

A recent systematic review confirms high levels of depression and anxiety in IDUs.⁷

Months in methadone program:

- The number of months in the methadone program has been shown to be related to methadone adherence.¹³

APRI-(as a noninvasive measure of hepatic fibrosis):

- APRI has been shown to have equal performance characteristics for fibrosis assessment compared to Fibrosis-4 index and Fibrosure.¹⁴

TSD (Treatment start date)

- An indicator variable specifying whether or not a participant initiated HCV treatment

Urban/rural

- Most participants on methadone reside in urban areas and the transportation requirements to obtain methadone may be important determinants of adherence.

Interaction (DAST-10) X months in methadone program

- DAST-10 is a measure of substance use and months in the methadone program is a measure of methadone adherence. The interaction between these two variables provides an indication of the degree to which substance use affects participants' lives and the potential effect of methadone.

Period

- Effect of study time period as a determinant of HCV treatment.

Site

- To account for clustering.

In total, five variables were affected by missing values, of which the outcome variable, SVR has the highest percentage of missing values at 40.6%. The lowest percentage of missing values was 1.99%, median of 3.49% [3.32%, 3.49%]. All missing values were imputed using MICE and for variables on ordinal and/or interval ratio scale, we used the predictive mean matching method. Diagnostics were used to compare agreement between imputed and observed data. eTable 2 presents descriptive statistics associated with the 20 imputed, per arm, datasets.

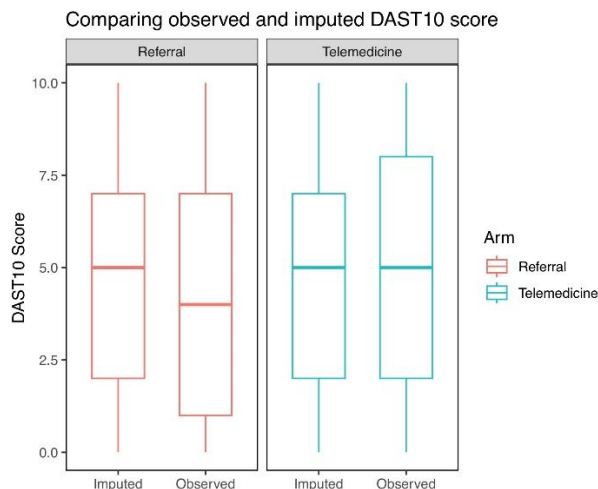
eTable 2: Descriptive statistics of sustained virological response associated with the 20 imputed datasets. The total number of participants is 602.

Arm	Minimum	Median (IQR)	Mean (SD)	Maximum
Usual care	38.5%	39.4% ([39.3%, 39.4%])	39.4% (0.32%)	39.7%
Telemedicine	88.6%	90.2% ([90.0%; 90.7%])	90.2% (0.52%)	91.0%

Abbreviations: IQR, interquartile range; SD, standard deviation

eFigure 2 presents the comparisons, per arm, of observed and imputed data for the DAST10 variable. eTable 3 presents the imputed and observed percentages (per category) for the variable illicit drug use.

eFigure 2: Distribution of imputed and observed Drug Abuse Screening Test (DAST10) levels per arm



eTable 3: Percentages of observed and imputed, per arm, illicit drug use per category as obtained by NIDA Quick Screen.

Category	Referral		Telemedicine	
	Observed	Imputed	Observed	Imputed
1	41.28%	34.64%	36.40%	34.29%
2	19.13%	20.00%	13.43%	20.00%
3	13.09%	16.43%	18.02%	17.86%
4	14.09%	13.57%	15.90%	12.85%
5	12.42%	15.36%	16.25%	15.00%
Total	100.00%	100.00%	100.00%	100.00%

eAppendix 2.2: Deaths

During the course of the study, we observed 13 deaths associated with excessive substance use, ten in the OTP-integrated facilitated telemedicine arm and 3 in referral (i.e., usual care) arm. Out of these 13 participants, ten did

not affect the main study outcome, i.e., SVR, as the HCV treatment outcome had already been obtained with nine participants obtaining an SVR and 1 participant was nonresponsive to therapy. eTable 4 presents data associated with the deceased participants in each category. The outcome of three patients who expired prior to SVR determination were subsequently imputed using the MICE algorithm. Therefore, deaths were handled as missing at random observations. Notice that the missing outcome death rate is 0.5% (3/602), and this event is unrelated to the study outcome. A participant who expires leaves the universe of interest, and the associated SVR outcome can be regarded as missing at random and, hence, imputed.¹⁵

eTable 4: Deceased participants by relevant demographic and residence location variables. Percentages are calculated using as a denominator the total number of deaths (n=13).

Study arm		SVR status			Age		Gender		Race		Ethnicity		Geographic	
Ref (%)	TM (%)	Yes (%)	No (%)	ND (%)	Mean (SD)	Median (IQR)	M (%)	F (%)	White (%)	Black/AA Other (%)	NH (%)	H (%)	U (%)	R (%)
3	10	9	1	3	55.5	57	8	5	7	6	12	1	11	2
23	77	69	8	23	9.26	[55,62]	61.5	38.5	53.9	46.1	92.3	7.7	84.6	15.4

Abbreviations: Ref, referral; TM, telemedicine; SVR, sustained virological response; ND, not determined; SD, standard deviation; IQR, interquartile range; M, male; F, female; AA, African-American; NH, Non-Hispanic, H, Hispanic; U, urban; r, rural.

eAppendix 3: Nonparametric Analysis

The nonparametric analysis for estimating the intervention (i.e., OTP-integrated facilitated telemedicine) effect is a cluster-level, robust, within-period method proposed by Thompson et al. (2018).¹⁶ This method does not require pre-specification of the correlation structure, which usually is not known in advance and avoids the assumptions that accompany the GLMM approach.

eAppendix 3.1: Cluster-level analysis:

We used the method proposed by Thompson et al.¹⁶ (and the associated R code) to estimate the intervention effect. This method does not use the entire data; it is, however, assumption-free. The estimate of the period-specific intervention effect expressed by the difference between the mean cluster-period percentage of participants who obtain SVR in OTP-integrated facilitated telemedicine and referral, computed by combining (using Rubin's rules) the results obtained from the 20 datasets is 58.6% (p-value <0.0001; 95% CI [44.0%, 74.1%]).

eAppendix 4: Effect modification

When time is treated as a continuous variable and the fitted model accounts for cluster random effect and arm effect, the results obtained using Rubin's combination rule on 20 separate data sets provide the same significant arm effect estimate with that obtained from the model in which time is treated as a discrete variable (i.e., the estimate of arm effect is 2.9, p-value <0.001, 95% confidence interval (2, 3.5). The time effect is nonsignificant. When the interaction term of time x arm is added, the estimate obtained is -0.002 with a 95% confidence interval of (-0.64, 0.64) and p-value = 0.5, indicating nonexistence of effect modification.

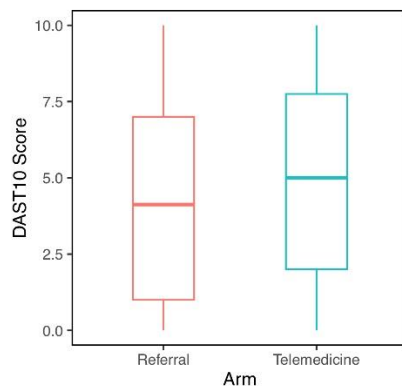
eAppendix 5: Selection Bias

Clustered randomized trials are susceptible to post-randomization selection bias because patient recruitment occurs after randomization.¹⁷ Furthermore, differential recruitment due to non-blinding nature of many clustered randomized trials, including our own, is a real possibility.

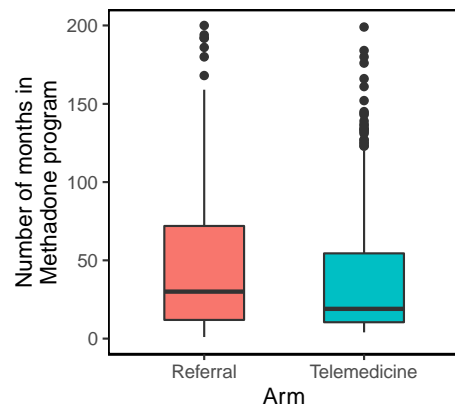
eAppendix 1 provides details on the precautions we took to avoid arm contamination.

We further illustrate below the baseline distribution of DAST10 scores in both referral (UC) and OTP-integrated facilitated telemedicine arms (eFigure 3) as well as similar distributions of the number of months in the methadone program (eFigure 4). These figures illustrate that the two arms are well balanced on both variables, illustrating comparability between the arms. DAST10, as a measure of drug use, is an important variable on which to establish comparability between the two arms since the majority of acute HCV infections occur in injection drug users.⁸ Furthermore, more than four fifths of the world's injection drug users use opioids.⁷ Similarly, months in the methadone program has been widely accepted as a measure of methadone adherence and stability.¹³

eFigure 3: Distribution of Drug Abuse Screening Test (DAST10) score in the referral (red) and opioid treatment program-integrated telemedicine (blue) arms.



eFigure 4: Distribution of the number of months participants are in the methadone program for the referral (red) and opioid treatment program-integrated telemedicine (blue) arms.



The direct acting antiviral medications prescribed in the study are illustrated in eTable 5. Most patients in both study arms were prescribed glecaprevir/pibrentasvir. Self-reported adherence to direct acting antiviral medication by week of treatment duration is illustrated (eTable 6) Of note, those individuals in the OTP-integrated facilitated telemedicine arm who did not achieve an SVR had <90% adherence during the last two study visits.

eTable 5: Direct acting antiviral medications prescribed to study participants

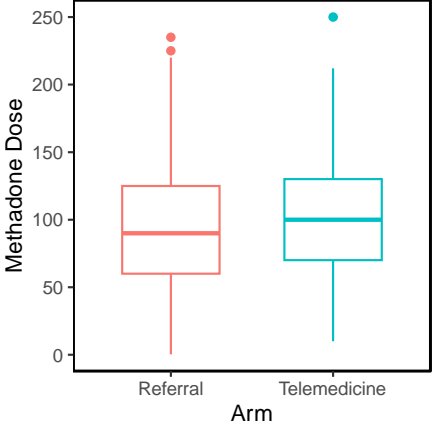
Direct Acting Antiviral	Referral (N=126)	Telemedicine (N=268)	Total (N=394)
Sofosbuvir/ledipasvir	7 (5.6%)	10 (3.7%)	17 (4.3%)
Glecaprevir/pibrentasvir	81 (64.3%)	175 (65.3%)	256 (65.0%)
Sofosbuvir/velpatasvir/voxilaprevir	2 (1.6)	10 (3.7)	12 (3.0%)
Velpatasvir/sofosbuvir	15 (12.0))	73 (27.2%)	88 (22.3%)
Elbasvir/grazoprevir	19 (15.1%)	0 (0.0%)	19 (4.8%)
Missing	2 (1.6%)	0 (0.0%)	2 (0.5%)

eTable 6: Adherence to direct acting antiviral medication by treatment week.

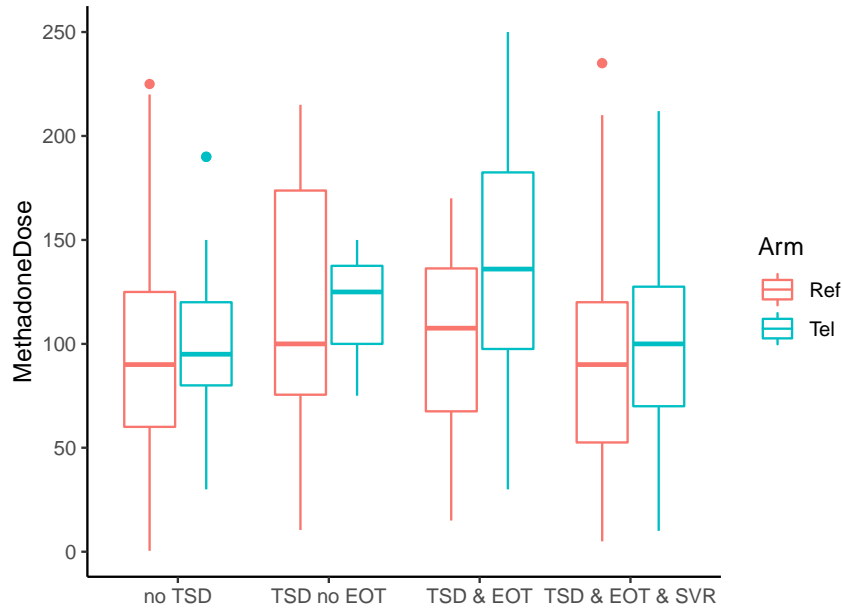
Visit Week	Usual Care		Telemedicine	
	SVR = Yes	SVR = No	SVR = Yes	SVR = No
Week 2	100	100	95.8	100
Week 6	96.4	100	97.9	80
Week 12	96	100	96.9	80

eFigure 5 presents the boxplots for graphical comparison of distributions of the methadone dose in participants in the referral and OTP-integrated facilitated telemedicine arms illustrating no differences in the doses between the two arms. eFigure 6 illustrates the distribution of methadone dose in participants without a treatment start date (i.e., no TSD), those with a treatment start date but without an end of treatment date (i.e., TSD no EOT), participants with TSD and EOT date, as well as those with TSD and EOT and SVR determination. The figure compared the distribution of the participants’ methadone dose between the arms. The two middle groups, i.e., participants with TSD and no EOT and those with TSD and EOT constitute the dropouts in the two arms. The figure indicates that there are no differences in methadone dose between the two arms in the no TSD and TSD and EOT and SVR groups. Retention in treatment with methadone is an acceptable measure of OUD treatment effectiveness, a key component of which is an adequate methadone dose.¹⁸

eFigure 5: Boxplots comparing the distribution of methadone dose in referral (red) and opioid treatment program-integrated telemedicine (blue) arms.



eFigure 6: Boxplots comparing methadone dose (mg/day) by study outcome in opioid treatment program-integrated telemedicine (blue) and referral (red) arms.



Abbreviations: TSD, treatment start date; EOT, end of treatment; SVR, sustained virological response.

eAppendix 6: Observations related to subgroups.

eTable 7 provides information on Hispanic individuals. Only 7.1% of Hispanic females initiated HCV treatment in referral and achieved SVR. In contrast, 88.56% of Hispanic females in OTP-integrated facilitated telemedicine achieved SVR (eTable 7). Furthermore, our data illustrate (eTable 8) that 100% of Hispanic females and 93.89% of Hispanic males are at least well versed in English.

eTable 7: Sustained virological response rate by period for Hispanic females in referral and opioid treatment program-integrated telemedicine arms

Study period	Referral	Telemedicine
1	1/16	0/0
2	1/11	3/3
3	0/1	10/11
4	0/0	10/12
Total	2 (7.1%)	23/26 (88.56%)

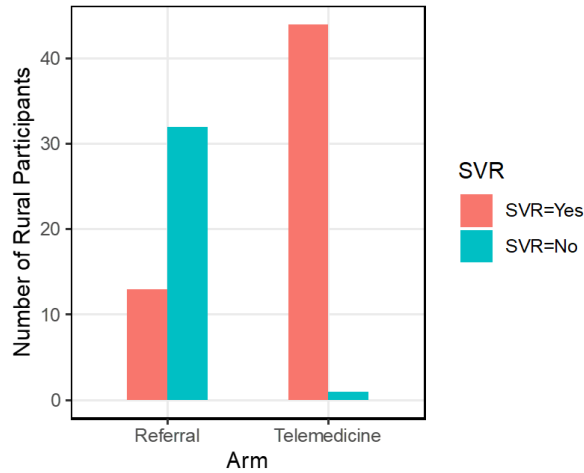
eTable 8: English language ability for Hispanic females and males

English level	Female Hispanics	Male Hispanics	Total
Not at all	0	2	2
Not well	0	6	6
Well	5	47	52
Very well	47	73	120
Missing value	2	3	5
Total	54	131	185

Facilitated telemedicine also favored a successful treatment outcome in participants who reside in rural areas. In the usual care arm, 28.89% of rural participants initiated HCV treatment and obtained an SVR. The remaining 71.11% did not initiate treatment and did not achieve SVR. In the OTP-integrated facilitated telemedicine arm, 100% of the

rural participants initiated HCV treatment and 97.78% obtained SVR (eFigure 7). The difference in response between the two arms necessitated the use of Bayesian methods for obtaining the confidence interval shown in Figure 3.

eFigure 7: Number of rural participants achieving a sustained virologic response stratified by study arm.



Abbreviation: SVR, sustained virologic response

eAppendix 7: Analysis of incidence rates

To assess the effect of the intervention on the outcome reference reinfection rates, we use the methods discussed in Bennett et al. (2002)¹⁹. Our analysis is unadjusted for covariates. We use RR_M (i.e., gives equal weight to each cluster). The estimate of the rate ratio is 1.24. To obtain the 95% confidence interval, we use 10,000 bootstrap samples of (d_{ij}, y_{ij}) , where d_{ij} is the number of reinfection cases in cluster j of reinfection group i and y_{ij} is the number of person-years of observation in cluster j of group i . Further, $i = 1, 2; j = 1, 2, \dots, 12$. The 95% confidence interval is (0.4, 5.9) and includes 1. Hence, there is a no difference between the two arms with respect to the reinfection rate.

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